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Multiple Hydrogen-Bond-Mediated Molecular Duplexes Based on the Self-Complementary Amidourea Motif

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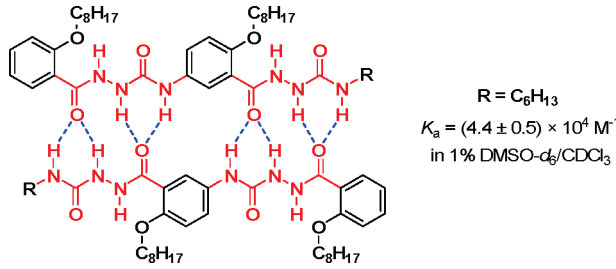
ABSTRACT



The self-complementary amidourea motif, which was stabilized by four intermolecular tricenter hydrogen bonds, was investigated in solution and in the solid state. Extensive studies on oligomer 2 indicated that the hydrogen-bonding mode could persist in longer molecular duplexes based on the amidourea motif. The dimerization constants of 2b·2b in various DMSO-d_6/$CDCl_3$ mixtures were determined quantitatively by ^1H NMR dilution studies, which suggested that the homoduplex was highly stable in low polar solvents.

In nature, cooperative action of many noncovalent forces not only leads to highly specific molecular recognition events and subsequently elegant functions but also renders well-defined three-dimensional structures of biomolecules.[1] Among the numerous biostructures, discovery of the double-helical structure of DNA[2] via hydrophobic effects, hydrogen bonds, and $\pi-\pi$ stacking interactions and elucidation of its function as genetic information carrier have laid the foundation for modern molecular biology.[3] Artificial construction of stable molecular duplexes from unnatural backbones is of fundamental importance for mimicking biomolecular structures and functions and can also be expected to have potential practical applications in materials science.[4] The development of such well-defined supramolecular architectures will be greatly facilitated if a diverse set of structural motifs with strong and specific intermolecular interactions becomes available.

Due to their strength, directionality, specificity, cooperativity, and reversibility, multipoint hydrogen-bonding motifs are the cornerstones of the biological recognition and assembly processes and increasingly feature in the design of functional organic materials and supramolecular polymers.[5] Inspired by nature's use of purines and pyrimidines as DNA base pairs, heterocycle-based multiple hydrogen-

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bonding modules (usually urea derivatives) are developed and have gained great success. In particular, Meijer's ureidopyrimidone (UPy) building block,[6] with its characteristics of high dimerization constant and synthetic accessibility, has found widespread applications in supramolecular chemistry, materials science, and catalysis.[7] Zimmerman's ureidodeazapterin[8] and ureidonaphthyridine[9] modules are also successful examples of heterocyclic building blocks. To address the tautomeric problem often accompanied with heterocycles, Gong et al. developed an aromatic oligoamide system.[10] Many other molecular duplexes assembled by arrays of amide units were also described.[11] In addition, Li et al. designed hydrazide-derived quadruply hydrogen-bonded heteroduplexes.[12] Recently, we reported systematic research of molecular duplex strands and noncovalent synthesis of shape-persistent cyclic hexamers based on the hydrazide hydrogen-bonding motif.[13]

As above-mentioned, most of the hydrogen-bond-mediated molecular duplexes were based on the amide, urea, and hydrazide units (Figure 1). However, the amidourea,[14] as another important hydrogen-bonding building block, has not gained much attention. Continuing our interest in developing unnatural molecular recognition systems, we herein report a

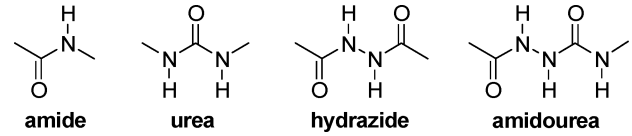

Figure 1. Chemical structures of several important hydrogen-bonding units.

new class of multiple hydrogen-bond-mediated molecular duplexes based on the self-complementary amidourea motif. To our knowledge, this work represents the first successful application of amidourea unit in the construction of molecular duplexes.

Compounds **1** and **2**, which possess one to two amidourea units, were designed and synthesized (Figure 2). The alkoxy

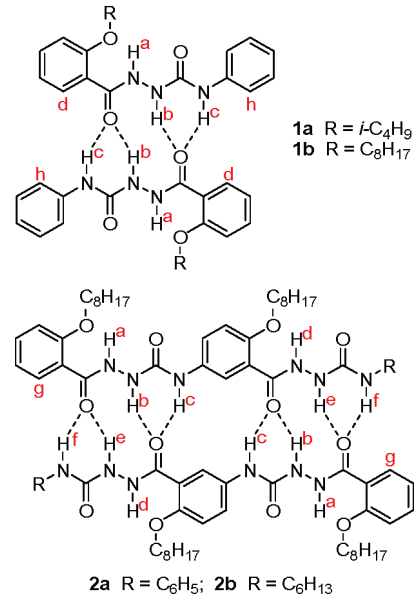

Figure 2. Chemical structures of **1** and **2** and representation of the molecular duplexes, with proton-labeling scheme indicated.

groups were incorporated for the formation of highly favorable S(6)-type[15] intramolecular hydrogen bonds, which should rigidify the backbones and preorganize the amidourea groups to facilitate the formation of molecular duplexes. Another advantage was improving solubility in organic solvents by the introduction of the octyloxy groups, as well as the hexyl group in **2b**. The synthesis is depicted in Scheme 1. Compound **1** was conveniently obtained in high yield by the reaction of hydrazide **3** with phenyl isocyanate. Compound **4**, which was prepared from hydrazide **3b** and 1,1′-carbonyldiimidazole efficiently, was refluxed with amine **5** in $CHCl_3$ to give compound **2** as a white solid.

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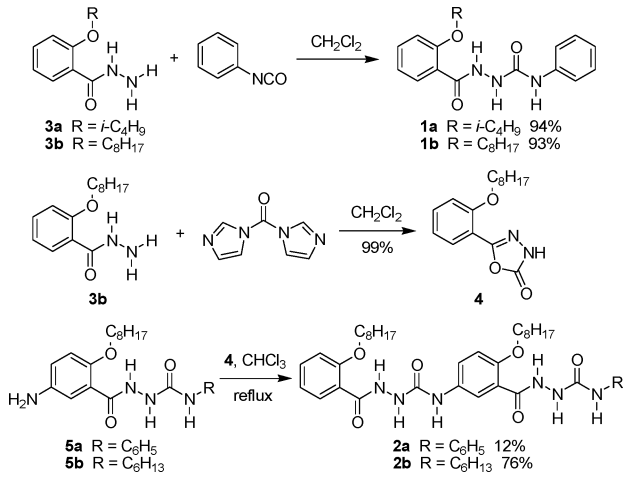
Scheme 1. Synthesis of Compounds **1** and **2**



A crystal of compound **1a**[16] suitable for X-ray crystallographic analysis was obtained by recrystallization from hot acetonitrile. Figure 3 shows the centrosymmetric homodimer

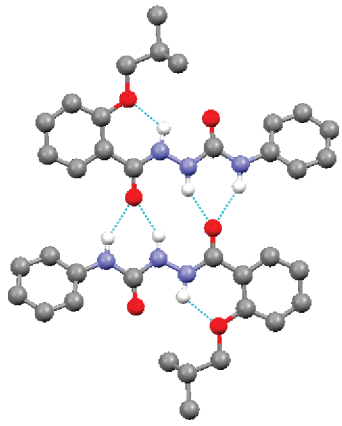


Figure 3. Crystal structure of **1a**, showing the dimeric binding motif. For clarity, only amidourea hydrogen atoms are shown.

motif **1a**·**1a** in the solid state. As expected, the dimer is stabilized by four intermolecular tricenter hydrogen bonds between the two amidourea skeletons. The distance of $NH^b\cdots O$ ($N\cdots O$ 2.81 Å, $H\cdots O$ 1.94 Å) is a little shorter than that of $NH^c\cdots O$ ($N\cdots O$ 2.92 Å, $H\cdots O$ 2.05 Å), which suggests that the $NH^b\cdots O$ hydrogen bond is slightly stronger than the $NH^c\cdots O$ hydrogen bond. In each molecule, an intramolecular S(6)-type hydrogen bond $NH^a\cdots O$ ($N\cdots O$ 2.61 Å, $H\cdots O$ 1.99 Å) is formed to rigidify the backbone.

^{1}H NMR studies of **1** in $CDCl_3$ revealed significant downfield shifts of the NH^a proton signals (10.41 ppm for **1a** and 10.49 ppm for **1b**, at 10 mM, 298 K), which suggested that the NH^a protons were involved in strong intramolecular hydrogen bonds. ^{1}H NMR binding studies were carried out in $CDCl_3$ by diluting a solution of **1** (from 25 to 1 mM). The NH^b and NH^c signals showed large concentration-dependent changes in their chemical shifts, supporting their roles in forming intermolecular hydrogen bonds. Nonlinear regression analysis[17,18] of the chemical shift data yielded dimerization constant K_{dim} values of $(2.5 \pm 0.3) \times 10^2$ M^{-1} for **1a**·**1a** and $(2.7 \pm 0.5) \times 10^2$ M^{-1} for **1b**·**1b**, respectively, which indicated that the dimers **1a**·**1a** and **1b**·**1b** had almost the same stability. Variable-temperature ^{1}H NMR studies[18] further supported the formation of the dimeric amidourea motif. Signals of NH^b (-1.33×10^{-2} ppm/K for **1a** and -1.38×10^{-2} ppm/K for **1b**) and NH^c (-7.83×10^{-3} ppm/K for **1a** and -8.02×10^{-3} ppm/K for **1b**), which were involved in the intermolecular hydrogen bonds, showed large temperature coefficients from 223 to 298 K, while signals of NH^a (-5.76×10^{-3} ppm/K for **1a** and -6.27×10^{-3} ppm/K for **1b**), which formed the intramolecular S(6)-type hydrogen bonds, showed much smaller temperature coefficients within the same temperature range. Two-dimensional NMR spectra[18] (NOESY, $CDCl_3$) provided the most diagnostic evidence for the homodimer structures of **1** in solution. Intermolecular contacts were observed between H^c and H^d, H^d and H^h for both **1a** and **1b**, which were fully consistent with the homodimer structures. More direct evidence for the dimerization came from ESI-MS studies.[18] In the mass spectra, signals corresponding to the dimers (677.56 for [**1a**·**1a** + Na]$^+$, calcd 677.31; 789.53 for [**1b**·**1b** + Na]$^+$, calcd 789.43) as base peaks were found.

Iterative extension of the self-complementary amidourea motif should lead to longer homoduplexes. The ^{1}H NMR spectra of compounds **2a** and **1b** in $CDCl_3$ are provided in Figure 4. Compared to the corresponding signals of NH

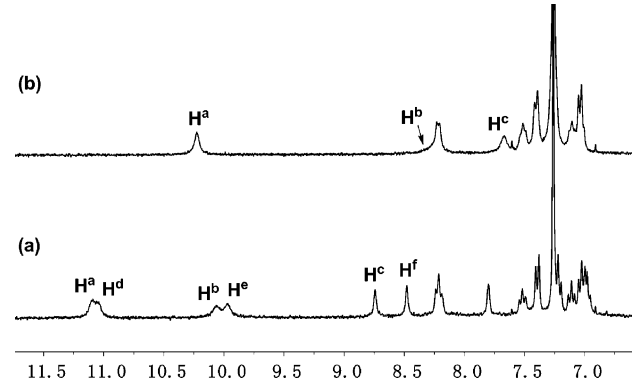


Figure 4. Partial ^{1}H NMR spectra (300 MHz) of (a) **2a** (2.0 mM) and (b) **1b** (2.0 mM) in $CDCl_3$ at 298 K.

protons of **1b**, all of the NH proton signals of **2a** shifted downfield substantially. This result clearly indicated that all

(16) Crystal data for **1a**: $C_{18}H_{21}N_3O_3$; $M_r = 327.38$; monoclinic; space group $P2(1)/c$; $a = 16.143(3)$ Å, $b = 6.4594(13)$ Å, $c = 17.674(4)$ Å; $\beta = 116.29(3)°$; $V = 1652.3(6)$ Å^3; $Z = 4$; $T = 173(2)$ K; 17945 reflections collected, 2981 unique; $R_1 = 0.0432$, $wR_2 = 0.1041$ [$I > 2\sigma(I)$]; $R_1 = 0.0511$, $wR_2 = 0.1083$ (all data).

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(18) See the Supporting Information for details.

the NH protons of **2a** were involved in much stronger hydrogen bonds and implied the formation of more stable molecular duplex. Unfortunately, we were unable to further study the self-assembly of **2a** for its poor solubility. Therefore, we extensively investigated the self-assembly of **2b** as a counterpart. The formation of the homoduplex was first confirmed by mass spectrometry.[18] In the ESI-MS of **2b**, signal corresponding to the dimeric structure (1416.64 for [**2b**·**2b** + Na]$^+$, calcd 1415.91) with considerable intensity was observed. When ^{1}H NMR dilution study of **2b** was performed in a $CDCl_3$ solution from 10.0 to 0.4 mM, no detectable changes were observed in the chemical shift values of all the NH protons. This showed that the dimerization of **2b** persisted at a low concentration in $CDCl_3$. Conservatively assuming that at 0.4 mM there was less than 10% dissociation that was not detected by ^{1}H NMR,[6b] the K_{dim} of duplex **2b**·**2b** was thus estimated to be a lower limit of 1.1×10^5 M^{-1} in $CDCl_3$. The fact that **2b**·**2b** is remarkably more stable than **1**·**1** strongly suggests an important cooperativity of the amidourea units in forming this series of molecular duplexes. Increasing the polarity of the solvent should decrease the binding stability of the duplex. Therefore, we studied the dimerization of **2b** in various DMSO-d_6/$CDCl_3$ mixtures. As shown in Table 1, the K_{dim} values of **2b**·**2b** were determined

Table 1. Dimerization Constants of the Duplex **2b**·**2b** in Various DMSO-d_6/$CDCl_3$ Mixtures at 298 K

DMSO-d_6/$CDCl_3$ (%)	K_{dim} (M^{-1})
1	$(4.4 \pm 0.5) \times 10^4$
3	$(4.5 \pm 0.4) \times 10^3$
5	$(7.1 \pm 0.2) \times 10^2$
7	$(2.3 \pm 0.1) \times 10^2$
10	$(9.6 \pm 0.3) \times 10$
15	$(3.1 \pm 0.1) \times 10$
20	$(1.5 \pm 0.1) \times 10$

quantitatively[17] in the range from 1% to 20% DMSO-d_6/$CDCl_3$ (v/v) mixtures by ^{1}H NMR dilution experiments (Figure 5). With more than 20% DMSO-d_6 in $CDCl_3$, dimerization of **2b** was too weak to be quantified by NMR. Unequivocal evidence for the formation of homoduplex **2b**·**2b** in solution was provided by NOESY study[18] in $CDCl_3$. Important cross-peaks were observed between H^b and H^e, H^g and H^f, which must correspond to intermolecular contacts between the two molecules constituting the homoduplex.

(19) The chemical shifts of the H^b signal of **2b** in 20% DMSO-d_6/$CDCl_3$ mixtures could not be recorded due to signal overlapping.

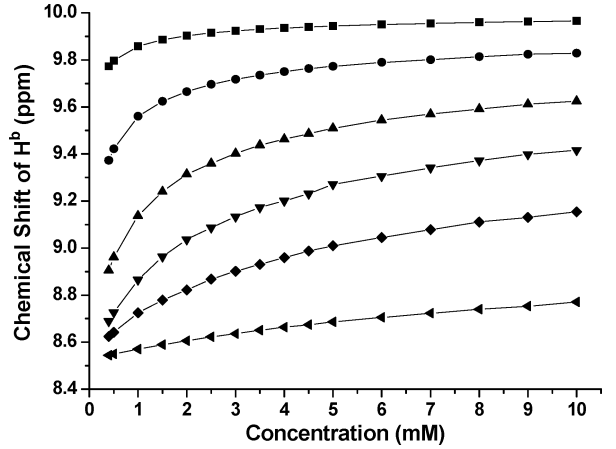

Figure 5. Complexation-induced chemical shift changes of H^b signal of **2b** in the concentration range from 0.4 to 10.0 mM in different solvent mixtures (from top to bottom: 1, 3, 5, 7, 10, and 15% DMSO-d_6 in $CDCl_3$)[19] at 298 K.

Thus, it is reasonable to propose that the longer homoduplex adopts a similar binding pattern to the amidourea motif **1**·**1**.

In conclusion, the self-complementary amidourea motif, which was stabilized by four intermolecular tricenter hydrogen bonds, was found in the solid state. And its dimeric structure and binding stability in solution was investigated. Iterative extension of the amidourea motif led to longer homoduplexes, in which the hydrogen-bonding mode could persist. The dimerization constants of **2b**·**2b** in various DMSO-d_6/$CDCl_3$ mixtures were determined quantitatively by ^{1}H NMR dilution studies, which indicated that the homoduplex was highly stable in low polar solvents. We believe that the results presented here provide new structural motifs useful in the construction of well-defined supramolecular systems and will lead to potential applications in materials science, studies of which are underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. Studies on the self-assemblies of **1a**, **1b**, and **2b**. X-ray crystallographic file (CIF) for compound **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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